## II. Remarks

### A. Status of Claims

Claims 1-8, 14-20, and 26-84 were pending and not-withdrawn when the November 1, 2006 Action was mailed to Applicant. Claims 1, 2, 8, 20, 26, 27, 31, 49, 58, and 76 have been amended herein without prejudice or disclaimer, with support for the amendments found in the specification as originally filed. Specific amendments are discussed in greater detail below. As correctly noted by the Action, the status of claim 20 was mislabeled in the August 16, 2006 Response to Notice of Non-Compliant Amendment; the current listing of claims reflects the correct status.

Claims 1-8, 14-20, and 26-84 are pending and under consideration.

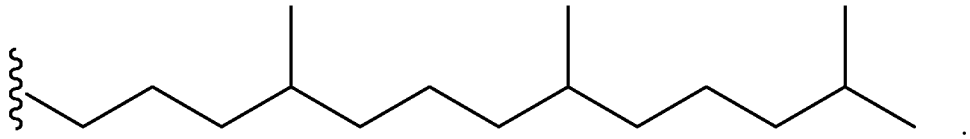
### B. Amendments to the Claims

Claims 1 and 26 are broadened by amending the proviso "$R^1$ can not be $-(CH_2)_{2-4}CO_2H$" to read "$R^1$ can not be $-(CH_2)_3CO_2H$." Similarly, claims 31 and 58 are broadened by amending the proviso "$R^1$ can not be $-(CH_2)_{2-3}CO_2H$" to read "$R^1$ can not be $-(CH_2)_3CO_2H$." Claims 2 and 27 are also amended to add the compounds 2,5,7,8-tetramethyl-(2R-(4R,8R,12-trimethyltridecyl)chroman-6-yloxy)**propionic acid** (compound 2, shown on page 25 of the specification) and 2,5,7,8-tetramethyl-(2R-(4R,8R,12-trimethyltridecyl)chroman-6-yloxy)**valeric acid** (compound 4, shown on page 27 of the specification) to the Markush groups. Support for all the above amendments is also found in the language of claim 1 (page 115) of parent application, Serial No. 09/502,592, as originally filed, which contains the phrase "$R^1$ is not **butyric acid**" (emphasis added). Compounds 2 and 4 are not obvious over Fariss *et al.*, 1994 (reference designation C3), cited in the Office Action dated February 21, 2001 in the prosecution

of parent application, Serial No. 09/404,001, now issued as U.S. Patent No. 6,417,223 (the '223 patent).

Claims 1 and 26 are further amended to correct a typo in the word pharmaceutical; claims 8 and 20 are amended to correct a typo in the word osteosarcomas, and claims 49 and 76 are amended to indicate the point of attachment of the chemical group. Support for the latter amendments is found, for example, in the structure of compound 1, shown on page 23 of the parent application, Serial No. 09/502,592, as originally filed.

Claims 1, 26, 31, and 58 were also amended to replace the term "phytyl" with the following structure:



Support for this change is found in Figure 2 of Serial No. 60/101,541, to which the present application claims priority. Claims 31 and 58 were further amended to remove the word "each." Claim 58 was still further amended to correct an improper dependency to claim 25.

**C. Response to Written Description Rejection**

The Action rejected numerous claims under 35 U.S.C. 112, first paragraph, asserting lack of support for $R^4$ being hydrogen. In an effort to further prosecution and secure prompt allowance, amendments have been made to independent claims, 1, 26, 31, and 58. As amended, $R^4$ is defined as methyl. Applicants, therefore, request that the written description rejections be withdrawn.

## D. Response to Enablement Rejection

The Action rejected all the presently pending claims under 35 U.S.C. 112, second paragraph. While the action concedes enablement for the treatment of colon and prostate cancer, it asserts that undue experimentation would be required for the general treatment of cancer. A common thread running through the arguments of this Action is that the Applicants must show animal testing results comparable to accepted treatments for each type of cancer covered by their claims. This position is problematic because it applies an incorrect legal standard to the enablement requirement. As discussed in detail below, this enablement rejection is not sustainable because (1) the level of skill in the art is high, (2) the detailed description of the invention (e.g. screening techniques, mechanistic insights, extensive results) provides ample guidance to a person of skill in the art, (3) the *in vitro* and *in vivo* test results, showing the ability of this invention to inhibit growth and/or induce apoptosis in at least fifteen different cancer cell types, and (4) the absence of any evidence that the invention is not enabled.

Applicants note that the specification demonstrates that the methods and compositions of this invention inhibit the growth and/or induce apoptosis in a wide variety of tumor cells. For example, the apoptotic $EC_{50}$ for a battery of test cancer cells for over twenty compounds of Applicants' invention are presented in Tables 1 and 2 of the specification (pages 90 and 91). These tables are reproduced here:

## TABLE 1

## Apoptosis Induced by Novel Tocopherol Compounds ($ec_{50}$ range μg/ml)

| Cell Type | VES | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Breast Cancer | | | | | | | | | | | | | | | | |
| HMEC | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | NT |
| MCF-10A | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | NT |
| MDA-MB-435 | 5-10 | 5-10 | 10-20 | 5-10 | N | N | N | 5-10 | 5-10 | 5-10 | N | N | 5-10 | N | N | 20-30 |
| MDA-MB-231 | 5-10 | 5-10 | 10-20 | 5-10 | N | N | N | 5-10 | 5-10 | 5-10 | N | N | 5-10 | N | N | 20-30 |
| MCF-7 | 10-20 | 5-10 | 20-30 | 20-30 | N | N | N | 10-20 | 10-20 | 10-20 | N | N | 5-10 | N | N | 20-30 |
| T47D | N | N | N | N | N | N | N | N | NT | NT | NT | NT | NT | NT | NT | NT |
| Cervical | | | | | | | | | | | | | | | | |
| ME-180 | 10-20 | 1-5 | 5-10 | 10-20 | N | N | N | 5-10 | 5-10 | 5-10 | N | N | 5-10 | N | N | N |
| Ovarian | | | | | | | | | | | | | | | | |
| C-170 | N | 10-20 | 10-20 | 10-20 | N | N | N | 10-20 | 10-20 | N | N | N | 10-20 | N | N | N |
| Endometrial | | | | | | | | | | | | | | | | |
| RL-95-2 | 10-20 | 10-20 | 10-209 | 10-20 | N | N | N | 5-10 | 1-5 | 5-10 | N | N | 5-10 | N | N | N |
| Prostate | | | | | | | | | | | | | | | | |
| PREC | N | N | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| LnCaP | 5-10 | 5-10 | 5-10 | 5-10 | N | N | N | 2.5-5 | 5-10 | 5-10 | N | N | >20-30 | NT | N | NT |
| PC-3 | 10-20 | 5-10 | 5-10 | 5-10 | N | N | N | 5-10 | 5-10 | 5-10 | NT | N | 10-20 | N | N | NT |
| DU-145 | 10-20 | 5-10 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Colon | | | | | | | | | | | | | | | | |
| HT-29 | 5-10 | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| DLD-1 | 10-20 | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Lung | | | | | | | | | | | | | | | | |
| A-549 | 20-30 | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Lymphoid Cells | | | | | | | | | | | | | | | | |
| Myeloma | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Raji | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Ramos | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Jurkat | 10-20 | 10-20 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| HL-60 | 10-20 | 5-10 | 10-20 | 10-20 | N | N | N | 5-10 | 10-20 | 10-20 | N | N | 20-30 | N | N | NT |

$EC_{50}$ μg/ml of tocopherol compounds 1-29 inducing 50% apoptosis; N = No apoptosis when treated for 2 days with 1-60 $EC_{50}$ μg/ml of tocopherol compounds 1-29; NT = Not tested; * = compounds exhibiting toxicity.

**TABLE 2**

**Apoptosis Induced by Novel Tocopherol Compounds ($EC_{50}$ range μg/ml)**

| Cell Type | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 39 | 42 | 43 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Breast Cancer | | | | | | | | | | | | | | | | | |
| HMEC | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| MCF-10A | NT | N | NT | N | N | N | NT | N | NT | N | N | NT | NT | NT | NT | NT | NT |
| MDA-MB-435 | N | NT | N | 10-20 | 10-20 | N | NT | N | N | N | 20-40 | NT | NT | NT | 10-20 | 10-20 | PPT. |
| MDA-MB-231 | N | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| MCF-7 | N | 10-20 | N | 10-20 | 5-10 | N | 15-20 | N | N | N | N | 10-20 | NT | NT | NT | NT | NT |
| T47D | NT | 10-20 | NT | N | 5-10 | NT | NT | NT | NT | NT | N | NT | NT | NT | NT | NT | NT |
| Cervical | | | | | | | | | | | | | | | | | |
| ME-180 | NT | 20-30 | N | 1-5 | 1-5 | 1-5 | NT | NT | NT | N | * | NT | NT | NT | NT | NT | NT |
| Ovarian | | | | | | | | | | | | | | | | | |
| C-170 | NT | 20-30 | N | 1-5 | * | N | NT | NT | NT | N | 20-30 | NT NT | NT | NT | NT | NT | NT |
| Endometrial | | | | | | | | | | | | | | | | | |
| RL-95-2 | NT | NT | NT | NT | NT | N | NT | NT | NT | N | 20-30 | NT | NT | NT | NT | NT | NT |
| Prostate | | | | | | | | | | | | | | | | | |
| PREC | NT | NT | N | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| LnCaP | NT | 10-20 | NT | 5-10 | 5-10 | N | NT | NT | N | N | 10-20 | 10-20 | NT | NT | NT | NT | NT |
| PC-3 | NT | NT | NT | N | 5-10 | N | NT | N | N | 20-30 | N | NT | NT | NT | NT | NT | NT |
| DU-145 | NT | NT | NT | 5-10 | 5-10 | N | NT | N | N | 20-30 | N | NT | NT | NT | NT | NT | NT |
| Colon | | | | | | | | | | | | | | | | | |
| HT-29 | NT | N | N | NT | NT | NT | NT | N | NT | N | N | NT | NT | NT | NT | NT | NT |
| DLD-1 | NT | NT | NT | NT | NT | NT | NT | NT | N | N | 20-40 | NT | NT | NT | NT | NT | NT |
| Lung | | | | | | | | | | | | | | | | | |
| A-549 | NT | N | N | 20-30 | 20-30 | NT | NT | NT | NT | NT | N | NT | NT | NT | NT | NT | NT |
| Lymphoid Cells | | | | | | | | | | | | | | | | | |
| Myeloma | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Raji | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Ramos | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Jurkat | NT | 10-20 | N | 10-20 | 10-20 | NT | NT | NT | NT | NT | 20-30 | NT | NT | NT | NT | NT | NT |
| HL-60 | NT | 10-20 | N | 10-20 | 10 | NT | NT | NT | NT | NT | N | NT | NT | NT | NT | NT | NT |

$EC_{50}$ μg/ml of tocopherol compounds 1-29 inducing 50% apoptosis; N = No apoptosis when treated for 2 days with 1-60 $EC_{50}$ μg/ml of tocopherol compounds 1-29; NT = Not tested; * = compounds exhibiting toxicity.

Tables 1 and 2 show that compounds of this invention were tested on six breast, one cervical, one ovarian, one endometrial, four prostate, two colon, one lung, and five lymphoid cell types. These tables indicate that the inventors have broadly tested the effectiveness of these compounds, significantly reducing the amount of experimentation needed for a person of skill in the art to practice the invention.

Furthermore, the inventors have disclosed in the examples section at least five different bioassays which can be employed to screen the compounds of this invention. The methods of performing the assays are described in detail in examples 7–11 specification as originally filed (pages 92-95). With the guidance provided by these examples, routine screening, not undue experimentation, is all that a skilled artisan would need to do in order to test the applicability of the efficacy of the compounds of this invention on other cancer cell types.

Furthermore, Applicants in their disclosure have gone significantly beyond the detection of anti-proliferative activity. They have also provided mechanistic insights as to how these compounds may induce apoptosis and/or inhibit the growth of cancer cells. For example, on page 95 of the specification, Applicants discuss the evidence indicating that the compounds of this invention induce apoptosis by means of three distinct apoptotic signaling pathways. Example 12 provides approximately three pages of experimental support for this conclusion. Similarly, in example 13, Applicants also provide mechanistic support for how the invention may exhibit additional anti-proliferative effects, such as induction of DNA-synthesis arrest, cell cycle arrest and cellular differentiation. The mechanistic insights provided in examples 12 and 13 provide valuable guidance, allowing a skill artisan to practice the full scope of the invention without undue experimentation.

In parallel with the *in vitro* cell culture and the mechanistic studies, the inventors further validated the effectiveness of the chroman ring compounds in studies using mouse model systems. For example, starting on page 99, Applicants describe in detail the methods and results using the MDA-MB-435 breast cancer model, the PC-3 prostate cancer model, and a skin cancer animal model. Then starting on page 101, Applicants describe in detail how the maximum tolerated dose (MTD) of one of the compounds of this may be determined, using α-TEA, a model chroman ring compound, as a specific example. Additional dosage information related to the *in vivo* studies is provided in Example 18 of the specification. Furthermore, starting on page 104, Applicants describe in detail how the chemotherapeutic effectiveness of one of the compounds would be determined, again using α-TEA as a specific example. For example, Tables 3 and 4 (see below) summarize some of the *in vivo* preclinical therapeutic studies of α-TEA (compound 1).

**TABLE 3**

MDA-MB-435 Human Breast Cancer Cells Transplanted in to Nude Mice

Mean tumor Weights (mg) Following Treatments

| Treatments | 1 | 4 | 7 | 10 | 14 | 17 | 21 |
|---|---|---|---|---|---|---|---|
| Vehicle | 70.1 | 98.2 | 119.5 | 153.2 | 172.8 | 203.7 | 226.1 |
| #1 (20 mg) | 70.1 | 85.8 | 123.9 | 127.9 | 147.2 | 143.8 | 179.4 |
| #1 (30 mg) | 68.1 | 85.7 | 97.3 | 98.4 | 126.6 | 118.7 | 125.2 |
| Taxol | 70.7 | 71.5 | 38.2 | 11.7 | 5.7 | 3.6 | 6.8 |

DU-145 Human Prostate Cancer Cells Transplanted into Nude Mice

Mean tumor Weights (mg) Following Treatments

| Treatments | 1 | 5 | 8 | 12 | 15 | 19 | 22 |
|---|---|---|---|---|---|---|---|
| Vehicle | 66.5 | 111.4 | 167.1 | 258.5 | 351.1 | 458.3 | 540.9 |
| #1 (20 mg) | 66.5 | 103.5 | 137.9 | 208 | 254.8 | 362.2 | 370.5 |
| #1 (30 mg) | 67.8 | 102.5 | 131.3 | 241.2 | 256.8 | 379.9 | 407 |
| Mitoxantrone | 66.8 | 107.2 | 141.1 | 185.4 | 205.2 | 325.3 | 389.4 |

HT-29 Human Colon Cancer Cells Transplanted into Nude Mice

Mean tumor Weights (mg) Following Treatments

| Treatments | 1 | 5 | 8 | 12 | 15 | 19 | 22 |
|---|---|---|---|---|---|---|---|
| Vehicle | 80.3 | 91.7 | 133.2 | 185.6 | 204.8 | 260.1 | 372.2 |
| #1 (20 mg) | 59.5 | 84.0 | 97.0 | 124.6 | 147.3 | 198.0 | 248.2 |
| #1 (30 mg) | 40.0 | 83.0 | 96.7 | 129.3 | 144.1 | 176.1 | 243.8 |
| 5-FU | 59.3 | 87.5 | 105.8 | 145.8 | 141.6 | 212.3 | 255.5 |

**Table 4:** Percent mean tumor weight gain (mg) following treatments

MDA-MB-435 Human Breast Cancer Cells

Percent Mean tumor Weight Gain (mg) Following Treatments[1]

| Treatments | 1 | 4 | 7 | 10 | 14 | 17 | 21 |
|---|---|---|---|---|---|---|---|
| Vehicle | 100 | 140.1 | 170.5 | 218.5 | 246.5 | 290.6 | 322.5 |
| #1 (20 mg) | 100 | 122.4 | 176.7 | 182.5 | 210.0 | 205.1 | 255.9 |
| #1 (30 mg) | 100 | 125.8 | 142.9 | 144.5 | 185.9 | 174.3 | 178.6 |
| Taxol | 100 | 101.1 | -46.0 | -83.7 | -91.8 | -99.5 | -90.3 |

DU-145 Human Prostate Cancer Cells

Percent Mean tumor Weight Gain (mg) Following Treatments

| Treatments | 1 | 5 | 8 | 12 | 15 | 19 | 22 |
|---|---|---|---|---|---|---|---|
| Vehicle | 100 | 167.5 | 251.3 | 388.7 | 528.0 | 458.3 | 689.2 |
| #1 (20 mg) | 100 | 155.6 | 207.4 | 312.8 | 383.2 | 362.2 | 544.7 |
| #1 (30 mg) | 100 | 151.2 | 193.7 | 355.8 | 378.8 | 379.9 | 560.3 |
| Mitoxantrone | 100 | 160.5 | 211.2 | 277.5 | 307.2 | 487.0 | 582.9 |

HT-29 Human Colon Cancer Cells

Percent Mean tumor Weight Gain (mg) Following Treatments

| Treatments | 1 | 5 | 8 | 12 | 15 | 19 | 22 |
|---|---|---|---|---|---|---|---|
| Vehicle | 100 | 152.1 | 220.9 | 307.8 | 339.6 | 431.3 | 617.2 |
| #1 (20 mg) | 100 | 141.2 | 163.0 | 209.4 | 247.6 | 332.8 | 417.1 |
| #1 (30 mg) | 100 | 139.5 | 162.5 | 217.3 | 242.2 | 296.0 | 409.7 |
| 5-FU | 100 | 147.6 | 178.4 | 245.9 | 247.2 | 358.0 | 430.0 |

[1]Percent Mean Tumor Weight Gain (mg) following treatment was determined by dividing the mean tumor weight at various time periods following treatment by the mean tumor weight at day 1 within the same treatment group and multiplying by 100.

These tables indicate that the effectiveness of α-TEA has been broadly tested *in vivo* using at least three different cancer cell models. Results such as these provide valuable guidance, thereby

significantly reducing the amount of experimentation needed for a person of skill in the art to practice the invention.

The Action suggests that because the Applicant disclosed some results appearing to show that compound 1 is less effective than Taxol that the claims may not be enabled for the treatment of breast cancer. Applicants note that the hurdle for enablement is not the same as the hurdle for obtaining Food and Drug Administration (FDA) approval to market a drug to the public. See *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). Indeed, 35 USC § 112, second paragraph does not condition patentability on a showing by the Applicants that their invention is better than other inventions. The evidence which Applicants have shown is sufficiently enabling. For example, the inventors have demonstrated that α-TEA reduces the human mammary tumor burden in mouse model systems and prevent metastasis of these cancer cells (see Table 3, above). Indeed the evidence provided throughout the specification, aspects of which have been highlighted above, provides sufficient evidence that the full scope of the claims have been enabled and that a person of skill in the art would not need to engage in undue experimentation to practice the present invention. Therefore, Applicant requests that the enablement rejections be withdrawn.

**E. Response to Non-Statutory Double Patenting Rejections**

The Action rejects the claims under the judicially created doctrine of obviousness-type double patenting over each of U.S. Patent No. 6,645,998 and Serial No. 10/695,275. Regarding the '998 patent, Applicants note that a terminal disclaimer will be submitted upon indication of allowable subject matter. Regarding the '275 application, Applicants note that a terminal disclaimer will be submitted upon indication of allowable subject matter, if needed in view of any issued claims from the '275 application.

## III. Conclusion

This is submitted to be a complete response to the November 1, 2006 Office Action. Further consideration of this case in view of the remarks contained herein is respectfully requested. No fees are believed due in this case; nonetheless, if it is determined that a fee is due in connection with this response, the Commissioner is authorized to deduct the required amount from Fulbright & Jaworski Deposit Account No. 50-1212/CLFR:177USD1, pursuant to 37 C.F.R. § 1.17. The Examiner is invited to contact the undersigned at (512) 536-3116 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Mark H. Voges/

Mark H. Voges
Reg. No. 58,112
Attorney for Applicants

FULBRIGHT & JAWORSKI, L.L.P.
600 Congress Ave., Ste. 1900
Austin, Texas 78701
(512) 536-3116
(512) 536-4598 (facsimile)

Date: February 1, 2007